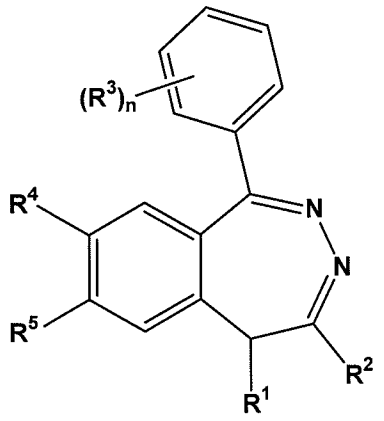
AMENDMENT OF THE CLAIMS

The following listing of claims replaces all prior listings of claims.

Listing of Claims:

1. (Previously Presented) A method of treating an individual afflicted with an inflammatory disorder of epithelial tissue comprising administering to said individual an effective amount of at least one compound according to Formula I:



I

wherein:

said at least one compound according to formula I is an (*R*)-enantiomer substantially free of its corresponding (*S*)-enantiomer, with respect to the absolute configuration at the 5-position of the benzodiazepine ring;

R^1 is -(C_1-C_7)hydrocarbyl or -(C_2-C_6)heteroalkyl;

R^2 is selected from the group consisting of –H, and -(C_1-C_7)hydro-carbyl;

wherein R^1 and R^2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring;

R^3 is independently selected from the group consisting of –O(C_1-C_6)alkyl, -OH, -O-acyl, -SH, –S(C_1-C_3)alkyl, $–NH_2$, -NH(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, -NH-acyl, $-NO_2$ and halogen;

n is 1, 2 or 3;

R^4 and R^5 are independently selected from the group consisting of –O(C_1-C_6)alkyl, -OH, O-acyl, -SH, –S(C_1-C_3)alkyl, $–NH_2$, NH-acyl and halogen;

wherein, R^4 and R^5 may combine to form a 5-, 6- or 7-membered heterocyclic ring;

or a pharmaceutically-acceptable salt of such a compound, wherein said compound is administered at a dose of less than about 50 mg/day.

2. (Original) The method according to claim 1, wherein said compound is administered at a dose of less than about 25 mg/day.

3. (Original) The method according to claim 1, wherein said compound is administered at a dose of less than about 10 mg/day.

4. (Original) The method according to claim 1, wherein said compound is administered at a dose of less than about 1 mg/day.

5. (Original) The method according to claim 1, wherein said compound is administered at a dose of less than about 10 mg/ml.

6. (Original) The method according to claim 1, wherein said compound is administered at a dose of less than about 1mg/ml.

7. (Original) The method according to claim 1, wherein said inflammatory disorder of epithelial tissue is a skin disorder.

8. (Original) The method according to claim 1, wherein said inflammatory disorder of epithelial tissue is a gastrointestinal disorder.

9. (Original) The method according to claim 1, wherein the compound is administered intracolonically or topically.

Claims 10-16. (Canceled)

17. (Previously Presented) The method according to claim 1, wherein:

R^1 is -(C_1-C_6)alkyl;

R^2 is selected from the group consisting of –H and -(C_1-C_6)alkyl;

R^3 is independently selected from the group consisting of –O(C_1-C_6)alkyl, -O-acyl and -OH;

n is 1, 2 or 3;

R^4 and R^5 are independently selected from the group consisting of –O(C_1-C_6)alkyl, -O-acyl and -OH, wherein, R^4 and R^5 may combine to form a 5-, 6- or 7-membered heterocyclic ring;

or a pharmaceutically-acceptable salt of such a compound.

18. (Original) The method according to claim 17, wherein:

R^1 is $-CH_2CH_3$;

R^2 is $-CH_3$

R^3, R^4 and R^5 are independently selected from the group consisting of –OH and –O(C_1-C_6)alkyl;

n is 1, 2 or 3;

or a pharmaceutically-acceptable salt of such a compound.

19. (Original) The method according to claim 18, wherein:

R^1 is $-CH_2CH_3$;

R^2 is $-CH_3$

R^3, R^4 and R^5 are independently selected from the group consisting of –OH and $-OCH_3$;

n is of 1, 2 or 3;

or a pharmaceutically-acceptable salt of such a compound.

20. (Original) The method according to claim 19, wherein the compound is selected from the group consisting of:

(*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

(*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine;

(*R*)-1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

(*R*)-1-(3-methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

(*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine;

(*R*)-1-(3-methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine;

(*R*)-1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine;

substantially free of the corresponding (*S*)-enantiomers;

and pharmaceutically acceptable salts thereof.

21. (Previously Presented) The method according to claim 20, wherein the compound is (*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

or a pharmaceutically acceptable salt thereof.

REMARKS

Entry of the response, reexamination, and reconsideration are requested in light of the following remarks.

Rejections and objections not reiterated are withdrawn. *See* 37 C.F.R. § 1.113(b); MPEP §§ 706.07, 707.07(e).

1. Status of the Claims

Claims 1-9 and 17-21 are pending and stand rejected. Claims 10-16 were canceled without prejudice or disclaimer in the response filed July 27, 2009.

2. Objection to the Claims

The claims are objected to, because there is no claim 15 in the claim listing filed July 27, 2009. The present amendment lists claim 15 as among the canceled claims, consistent with the amendment July 27, 2009. The present amendment thus is believed to fully address the grounds for objection. The objection thus may be withdrawn.

3. Rejection under 35 U.S.C. § 103

Claims 1-9 and 17-21 are rejected under 35 U.S.C. § 103[1] as allegedly obvious over Ito, *Iyakuhin Kenkyu* 12: 587-600 (1981) ("Ito") in view of U.S. Patent No. 6,093,740 ("Jirousek").

The Ito reference:

The Office Action incorporates the teachings of Ito set forth in previous Office Actions by reference. The issue is what those teachings would have suggested to the artisan at the time of the invention. In this regard, the Office continues to allege that the elevation of pain thresholds by tofisopam is relevant to the issue of obviousness of the present claims. It is unclear how or why. Even if the artisan would have been motivated to administer tofisopam to an

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[1] The Office Action inadvertently mentions Section 102(a) at the top of page 3. Clarification is requested in the next communication.

individual to elevate their pain threshold, the Office does not explain why this would have motivated the artisan to administer tofisopam to an individual afflicted with an inflammatory disorder of epithelial tissue, as claimed.

Presumably, the Office is of the (unstated and unsubstantiated) opinion that inflammatory disorders are painful, and that the artisan would have been motivated to administer compounds that reduce pain. There are two problems with this inference. First, Ito teaches that tofisopam "had no surface or infiltrative anesthetic activity," suggesting it has no direct role in pain reduction. Second, Ito indicates that the pain threshold can be increased only at the relatively high dose of 1,000 mg/kg body weight, which vastly exceeds the claimed administration dose of "less than about 50 mg/day." Accordingly, the artisan would not have been motivated by the teachings of Ito to practice the claimed method, when the teachings Ito are considered as a whole.

The Office Action at page 5 reiterates Ito's teachings, without explaining the relevance of those teachings. The rejection as stated relies only on the increase in pain threshold mentioned at page 3 of the Office Action, which Applicants address above. The rejection no longer relies on tofisopam's other effects, e.g., its effect on spontaneous locomotion. Applicants argued in their July 27, 2009, response that these other effects would not have suggested the claimed invention. By failing to address Applicants' arguments, the Office implicitly concedes this conclusion.

The meaning of "less than about 50 mg/day":

Regarding the remarks at page 5 on the effect on tofisopam on pain threshold, the Office alleges that the broadest reasonable interpretation of "about" encompasses a dosage within the range taught by Ito. Ito teaches a dosage of 1000 mg/kg body weight. The claimed dosage is less than about 50 mg/day. The Office's reviewing courts have held repeatedly that the "broadest reasonable interpretation" of claim terms must be consistent with the specification and the plain language of the claims. *See, e.g., In re Suitco Surface Inc.*, 603 F3d 1255, 94 USPQ2d 1640, 1644 (Fed. Cir. 2010) ("The broadest-construction rubric coupled with the term 'comprising' does not give the PTO an unfettered license to interpret claims to embrace anything

remotely related to the claimed invention."). The Office presents no evidence that a dosage of 1000 mg/kg body weight is even remotely related to a dosage of less than about 50 mg/day. Further, the specification makes it clear that "less than about 50 mg/day" ***must*** be less than 100 mg/day. *See, e.g.*, pages 43 and 46 of the specification. The Office's interpretation of "less than about 50 mg/day" is inconsistent with both the plain language of the claims and with the specification. For these reasons, the Office's interpretation is unreasonable.

The combination of Ito and Jirousek:

The Office combines the teachings of Ito and Jirousek. It is well established that obviousness rejections are based on combinations of references and cannot be rebutted simply by attacking one of the references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Applicants thus direct the following remarks to the combination of Ito and Jirousek.

The Office alleges that Jirousek teaches administering a compound structurally similar to the compound of Formula I. For the reasons set forth on page 10 of Applicants' response filed July 27, 2009, Jirousek teaches different compounds than the compound of Formula I. This evidence is undisputed on the record. The rejection specifically relies on Jirousek for teaching that these compounds are useful in treating dermal edema.

The Office alleges that it would have been obvious to modify Ito in view of Jirousek. The rejection assumes the artisan would have modified Ito to use instead the compound of Jirousek to treat dermal edema. Even if this were true, it is unclear how this relates to the claims. The claims are directed to the use of a compound of Formula I, not the compound of Jirousek.

If the Office meant to state that the artisan would have used the compound of Ito for Jirousek's purpose of treating dermal edema, the rejection is still improper. The Office alleges that the artisan would have been motivated to use Ito's and Jirousek's compounds interchangeably, because they are structurally similar. But the two compounds are ***not*** interchangeable. Ito clearly states at p. 588, ¶5, that his compound has no effect on paw edema formation. This teaching is ***undisputed on the record.*** The reasoning behind this version of the rejection is that the artisan, realizing the deficiencies of Ito's compounds in treating edema,

would nevertheless have been motivated to use Ito's compounds, in view of Jirousek's treatment of edema with different compounds. There is no reason to combine the references. The rejection is not supported by a rational underpinning.[2]

The Office cites case law regarding enantiomers. Applicants do not concede the correctness of the Office's assertions or allegations in this regard. The combination of Ito and Jirousek does not render the claims obvious for the reasons above. It is unnecessary to reach the issue of whether the combined references additionally would have suggested the claim element of

> said at least one compound according to formula I is an (*R*)-enantiomer substantially free of its corresponding (*S*)-enantiomer, with respect to the absolute configuration at the 5-position of the benzodiazepine ring.

Accordingly, the rejection is unsubstantiated and must be withdrawn. The claims must be allowed.

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2 "[R]ejections on obviousness grounds [must include] some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329 (Fed. Cir. 2006), *cited with approval in KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418, 82 USPQ2d 1385 (2007).

CONCLUSION

The application is believed to be in condition for allowance, and Applicants respectfully request indication of the same. Should any issues remain outstanding or if there are any questions concerning this paper, or the application in general, the Examiner is invited to telephone the undersigned representative at the Examiner's earliest convenience. This paper may be used as a constructive petition for an extension of time. If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0573.

Respectfully submitted,

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Date : Sept 17, 2010

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